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United Research Laboratories, Inc.
Mutual Pharmaceutical Company, Inc.

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March 6, 2001

Dockets Management Branch
Food and Drug Administration (HFA-305)
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Citizen Petition

Dear Sir or Madam:

The undersigned submits this petition, in quadruplicate, in accordance with 21 CFR 10.30 requesting that the Food and Drug Administration (FDA), among other things, withhold approval of any abbreviated new drug application (ANDA) for a duplicate version of Skelaxin® (Metaxalone) Tablets, 400 mg without an acceptable *in-vivo* fasting bioequivalence study demonstrating that the proposed test product and the reference product are bioequivalent.

A. Action Requested

Based on information presented herein, the petitioner requests that the FDA rescind a previous determination that Metaxalone Tablets is a drug product not presenting bioequivalence problems and announce publicly in the Orange Book that an *in-vivo* fasting bioequivalence study will be required as a condition of approval of any ANDA for a generic version of a solid oral dosage form of Metaxalone. The petitioner also requests that the Office of Generic Drugs (OGD) not approve any ANDA for a generic version of Metaxalone that does not contain the results of an acceptable *in-vivo* fasting bioequivalence study.

B. Statement of Grounds

Mutual Pharmaceutical Company, Inc. (Mutual) first became interested in developing the generic version of Metaxalone Tablets in April of 1998. An acceptable source of Metaxalone Active Pharmaceutical Ingredient (API) was located and the first lot of API to be used in the manufacture of Metaxalone Tablets was obtained in September 1998. Over the next 12 months, Mutual pursued a Formulation Development Program designed at establishing a test product formulation that had similar *in-vitro* dissolution characteristics as that of the innovator product (Skelaxin®). The dissolution method chosen, based on the low solubility of Metaxalone, utilized an aqueous 2% sodium lauryl sulfate (SLS) medium (1000 mL per vessel, USP apparatus II at 75 rpm).

The first Exhibit Lot No. BB5800040[1] (BB'40) and the innovator product showed release rates of >80% after 60 minutes. The innovator product was observed to have a slower release rate at earlier time points (Attachment No. 1).

Because of the slow dissolution characteristics of the innovator, Mutual initially believed that the FDA would require an *in-vivo* study as a condition of approval for Metaxalone products. Therefore, once a test formulation was developed that produced similar dissolution characteristics to the innovator product, Mutual contracted with a contract research organization to perform a fasting *in-vivo* bioequivalence study, which was dosed on October 23, 1999.[2]

Despite the test product's more rapid dissolution at the earlier time points, the Cmax and AUC of the reference product were greater. In addition, the 90% confidence intervals of the log transformed data for the bioequivalence parameters Cmax and AUC_{inf} failed (55.5 – 84.5% and 77.2 – 93.4% respectively). (Attachment No. 2)

The product was reformulated in an attempt to correct for the differences seen in the first *in-vivo* study. That resulted in the manufacture of Exhibit Lot No. BB5800047 (BB'47) on May 8, 2000. The *in-vitro* dissolution profiles (utilizing the same methodology, as described above) of the test and reference products more closely resembled one another (Attachment No. 3). In this case, the test and reference products released >80% in 90 minutes.

In addition to the dissolution testing mentioned above, and because of the lack of correlation of *in-vitro* and *in-vivo* data seen in the first study, Mutual sought to develop an additional R&D type dissolution test that would be more discriminating during the formulation optimization process in an effort to better characterize the difference in dissolution among its two test formulations and the innovator. The new, more discriminating dissolution test employed an aqueous 0.25% SLS (500 mL per vessel (peak), using USP apparatus II at 25 rpm). While recognizing that this test could not be used for a routine quality control release test, this test detected the difference noted in the first *in-vivo* study. For instance, under these conditions, Exhibit Lot No. BB'40 showed slower dissolution rates in this medium, as compared to the commercially available product. The reformulated product Exhibit Lot No. BB'47, however, showed dissolution profiles that were almost superimposable to the innovator under these test conditions (Attachment No. 4). With this information in hand, Mutual initiated another *in-vivo* fasting bioequivalence study employing Lot No. BB'47 in comparison with the innovator product. This study was dosed on May 21, 2000.[3]

[1] The exhibit lots manufactured for purposes of the testing outlined in this document were both batches of approximately 200,000 tablets.
[2] This study was conducted as a pivotal bioequivalence study and had an N=35.
[3] This study was conducted as a pivotal bioequivalence study and had an N=24.

Once again the test and reference products were **not** bioequivalent. The geometric mean ratio for Cmax (Test/Reference) was equal to 231.64% and the 90% confidence intervals of the log transformed data for the bioequivalence parameters Cmax and AUC_{inf} failed (202 - 266% and 124 – 154%, respectively) (Attachment No. 5).

The results were quite surprising, and this left the company in a lurch in terms of formulation development, specifically, because there did not appear to be any correlation between *in-vitro* dissolution and *in-vivo* performance of the products.

On or about January 19, 2001, Mutual became aware that the FDA was considering Metaxalone Tablets a "non-bio problem" drug, thereby requiring only a request for waiver of *in-vivo* bioequivalence study requirements accompanied by acceptable comparative *in-vitro* dissolution profiles to meet ANDA bioequivalence approval criteria. This information was independently confirmed by Mutual with the FDA on January 22, 2001. Had Mutual been cognizant of the Agency's position in regard to bioequivalence requirements for this drug product when developmental work first began in 1998, we would likely have never commissioned a bioequivalence study. Rather, Mutual would have filed an ANDA containing a request for waiver of *in-vivo* bioequivalence study requirements based on comparative dissolution profiles. Based on average ANDA approval times, it is highly likely that we would have obtained FDA approval by now for one of our test formulations, neither of which would have been bioequivalent to the innovator product.

Mutual developed two formulations with dissolution profiles similar to that of the innovator product. It is clear that neither of the Mutual test formulations could have been found to be bioequivalent to the innovator product. One test formulation failed on the low end of *in-vivo* performance that may impact on product efficacy and one test formulation failed on the high end of *in-vivo* performance that may impact on safety considerations. Nonetheless, under current Agency thinking, as we understand it, for this drug either of the Mutual test formulations might have been approved.

The labeling of the reference-listed drug product identifies the most frequent reactions to Metaxalone as nausea, vomiting, gastrointestinal upset, drowsiness, dizziness, headache, and nervousness or "irritability". Either the rate or extent of drug absorption typically mediates such adverse events. Mutual has demonstrated through the conduct of two *in-vivo* bioequivalence studies that reliance upon *in-vitro* dissolution as a predictor of *in-vivo* performance is not possible. The public health implications of this finding are clear, especially if the FDA maintains its current position on Metaxalone.

One reason that Mutual assumed that OGD would require *in-vivo* studies as a subject of ANDA approval was based on the low solubility and poor dissolution performance of Metaxalone Tablets. The regulations at 21 CFR 320.33(e)(1) and (2) outline physicochemical criteria that if identified in a product could provide sufficient evidence that a drug product had an actual or potential bioequivalence problem.

To be more specific, 320.33(e)(1) cites a solubility of less than 5 mg/mL as a criterion of evidence that an actual or potential bioequivalence problem may exist. Mutual has conducted recent experiments that demonstrate that the solubility of Metaxalone in water (the medium referenced in the above-cited regulation) is only 0.3 mg/mL (Attachment No. 6). Clearly, Metaxalone fails to pass this specific regulatory hurdle.

Secondly, 320.33(e)(2) refers to the rate of dissolution in water under specific conditions as another criterion. That is, the product may be considered to present actual or potential bioequivalence problems if "the dissolution rate of one or more products is slow, e.g., less than 50% in 30 minutes when tested using either a general method specified in an official compendium, or a paddle method at 50 revolutions per minute in 900 milliliters of distilled or deionized water at 37°C". Mutual's test results are appended at Attachment No. 7. As can be seen, both the test and reference products had very "slow" dissolution under the conditions described in the regulation cited above. The dissolution for each product was not only less than 50% at 30 minutes, it was less that 50% at 120 minutes! This is clearly an indication that Metaxalone Tablets represents a drug product with actual or potential bioequivalence problems.

Of particular concern is that the test results for Mutual's Lot No. BB'47, the lot that demonstrated a 234% increase in Cmax, actually dissolved at a much slower rate than the innovator product. This further supports the contention that there is no relationship between *in-vitro* dissolution performance and *in-vivo* bioavailability.

Mutual has performed *in-vivo* tests and a variety of *in-vitro* tests on both the test and reference products. The results of these tests demonstrate that dissolution is not predictive of *in-vivo* performance and the *in-vitro* tests results failed to support, from a regulatory or public health perspective, any other determination except that Metaxalone Tablets should be classified as a bio problem drug.

Mutual, therefore, requests that the FDA:

1. Reclassify Metaxalone Tablets as a drug product for which potential or actual bioequivalence problems exist.
2. Make a public announcement of its decision to do so in the Orange Book.
3. Require an *in-vivo* fasting bioequivalence study as a condition of approval of an ANDA.
4. Not approve any ANDA until such time as the application contains the results of an acceptable contains the results of an acceptable *in-vivo* fasting study.

Please feel free to contact Mutual directly at the number provided below, if any additional information is required for you to reach a decision in this matter.

C. Environmental Impact

The petitioner claims a categorical exclusion under 21 CFR 25.31.

D. Economic Impact

Mutual does not believe that this is applicable in this case, but will agree to provide such an analysis, if requested by the Agency.

E. Certification

Mutual certifies, that to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner, which are unfavorable to the petition.

Respectfully submitted,

Robert Dettery
Vice President, Regulatory Affairs
Mutual Pharmaceutical Company
Telephone 215-288-6500

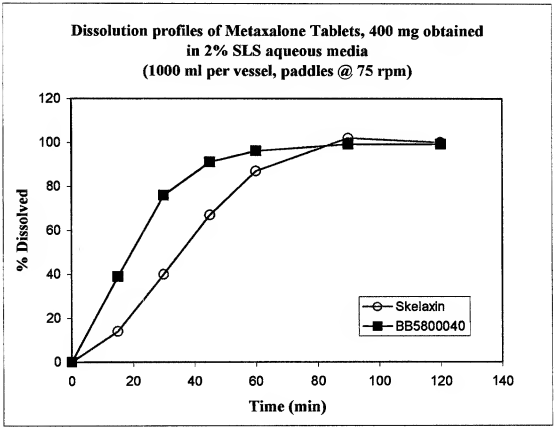
Attachments

Cc: G. Buehler, Acting Director, HFD-600
J. Bull, MD Director, HFD-550

ATTACHMENT 1

Dissolution Profiles of Metaxalone Tablets, 400 mg (Skelaxin vs. BB5800040) in 2% SLS aqueous media

Time (min)	Skelaxin	%RSD	BB5800040	%RSD
0	0	0	0	0
15	14	3	39	37
30	40	4	76	23
45	67	5	91	9
60	87	2	96	3
90	102	3	99	1
120	100	2	99	2



ATTACHMENT 2

In Vivo plasma concentrations after single dose of Metaxalone Tablet, 400 mg Lot #BB5800040, and Summary of Statistical Analysis

A RELATIVE BIOAVAILABILITY STUDY OF 400 MG METAXALONE TABLETS UNDER FASTING CONDITIONS

Mutual Pharmaceutical Company, Inc
11000 Orthodox Street
Philadelphia, PA 19124-3131

PRACS Study Number P99-466

December 20, 1999

PRACS Institute, Ltd.
2615 North University Drive
Fargo, ND 58102
(701) 239-4750

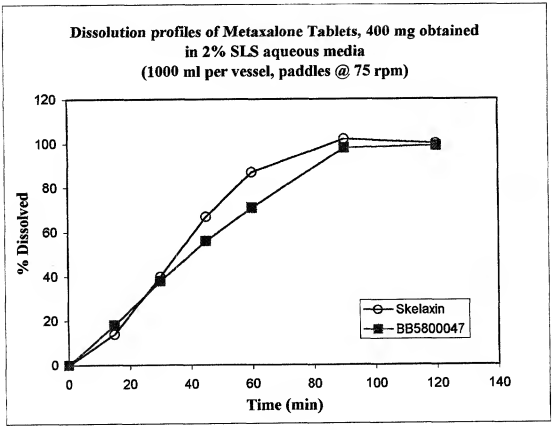
Brenda L. Krogen, M.S.
Statistician

ATTACHMENT 3

Dissolution Profiles of Metaxalone Tablets, 400 mg (Skelaxin vs. BB5800047) in 2% SLS aqueous media

Metaxalone Tablets, 400 mg

Time (min)	Skelaxin	%RSD	BB5800047	%RSD
0	0	0	0	0
15	14	3	18	4
30	40	4	38	4
45	67	5	56	5
60	87	2	71	6
90	102	3	98	1
120	100	2	99	1



In Vivo plasma conc. after single dose of Metaxalone Tablet, 400 mg. Lot #BB5800040

	0.00	0.50	1.00	1.50	2.00	2.50	3.00	3.50	4.00	5.00	6.00	8.00	12.00	16.00	24.00	30.00	36.00	48.00
Test	0.00	39.55	144.09	218.13	277.91	323.77	347.02	377.05	378.94	344.48	310.64	201.02	128.59	88.38	62.73	32.17	13.55	3.63
SD	0.00	42.17	150.67	213.12	250.15	253.15	277.37	272.64	257.24	223.00	215.41	157.77	131.77	53.12	32.15	26.99	12.59	5.42
Ref	0.00	20.00	124.10	261.21	377.74	441.83	485.65	484.80	507.75	472.37	404.98	236.59	139.46	98.08	64.14	26.25	8.50	3.04
SD	0.00	22.72	163.80	285.01	339.90	360.72	329.41	287.71	235.90	195.26	170.40	117.31	87.01	61.52	30.95	17.25	9.27	7.43

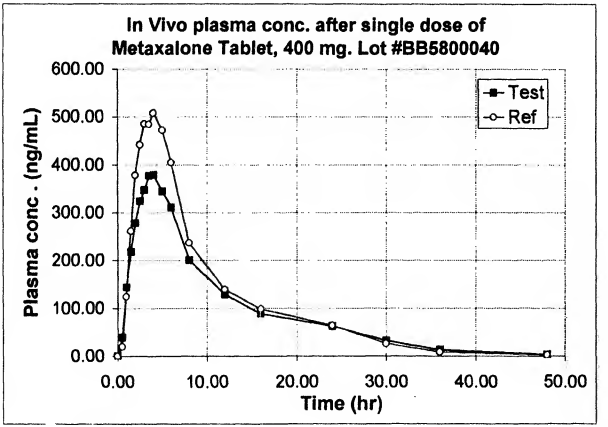


Table 4
Summary of Statistical Analysis
N=35

Log-Transformed Data

PK Variable	Least Squares Mean		Geometric Mean			Mean Square Error	Standard Error	90 % Confidence Interval (Lower Limit, Upper Limit)	P-values for ANOVA Effects		Power of ANOVA
	Test	Reference	Test	Reference	% Ratio				Product	Period	
C_{max}	6.052	6.430	424.96	620.17	68.52	0.2611	0.1239	(55.5, 84.5)	0.0045	0.6204	0.4155
AUC_{0-t}	8.277	8.473	3932	4784	82.19	0.0533	0.0560	(74.8, 90.4)	0.0014	0.9735	0.9715
AUC_{inf}	8.342	8.505	4196	4939	84.96	0.0534	0.0560	(77.2, 93.4)	0.0064	0.6354	0.9713

Non-Transformed Data

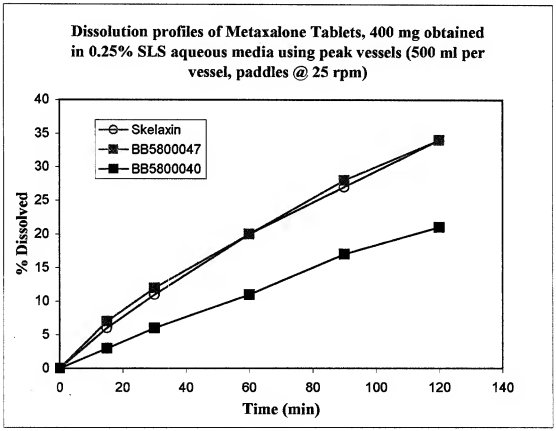
PK Variable	Least Squares Mean				Mean Square Error	Standard Error	90 % Confidence Interval (Lower Limit, Upper Limit)	P-values for ANOVA Effects		Power of ANOVA
	Test	Reference	Difference	% Ratio				Product	Period	
C_{max}	517.92	669.29	-151.37	77.38	64586.4766	61.6377	(61.8, 93.0)	0.0197	0.4826	0.5582
T_{max}	3.69	3.43	0.26	107.58	1.7748	0.3231	(91.8, 124)	0.4187	0.1111	0.5387
AUC_{0-t}	4365	5074	-709.00	86.03	1021692.5588	245.1521	(77.9, 94.2)	0.0068	0.7177	0.9799
AUC_{inf}	4569	5215	-646.00	87.61	1084073.6746	252.5253	(79.4, 95.8)	0.0154	0.5101	0.9795
k_{elim}	0.1116	0.1157	-0.0041	96.46	0.0011	0.0081	(84.6, 108)	0.6158	0.9289	0.7900
$t_{1/2}$	7.75	6.66	1.09	116.37	21.5707	1.1264	(87.7, 145)	0.3397	0.7746	0.2091

Geometric means are based on least squares means of log transformed values.

ATTACHMENT 4

Dissolution Profiles of Metaxalone Tablets, 400 mg (Skelaxin vs. BB5800047 and BB5800040) in 0.25% SLS aqueous media using peak vessels

Time (min)	Skelaxin	%RSD	BB5800040	%RSD	BB5800047	%RSD
0	0	0	0	0	0	0
15	6	7	3	7	7	9
30	11	10	6	6	12	6
60	20	7	11	6	20	5
90	27	9	17	4	28	4
120	34	11	21	2	34	2



ATTACHMENT 5

In Vivo plasma concentrations after single dose of Metaxalone Tablet, 400 mg. Lot #BB5800047, and Summary of Statistical Analysis

A RELATIVE BIOAVAILABILITY STUDY OF 400 MG METAXALONE TABLETS UNDER FASTING CONDITIONS

Mutual Pharmaceutical Company, Inc.
11000 Orthodox Street
Philadelphia, PA 19124-3131

PRACS Study Number P99-642

July 7, 2000

PRACS Institute, Ltd.
2615 North University Drive
Fargo, ND 58102
(701) 239-4750

Brenda L. Krogen, M.S.
Statistician

In Vivo plasma conc. after single dose of Metaxalone Tablet, 400 mg. Lot #BB5800047

	0.00	0.50	1.00	1.50	2.00	2.50	3.00	3.50	4.00	4.50	5.00	6.00	8.00	12.00	16.00	24.00	30.00	36.00	48.00
Test	0.00	89.22	385.54	762.85	1033.75	1289.12	1352.38	1407.92	1365.35	1287.16	1154.78	793.80	373.57	84.89	26.93	5.94	2.30	0.54	0.00
SD	0.00	118.88	456.68	664.23	688.52	630.30	689.36	602.33	609.33	674.02	673.63	531.31	308.38	80.33	28.02	10.41	6.51	2.63	0.00
Ref	0.00	16.55	99.05	235.30	350.34	467.54	509.28	542.92	551.67	580.05	576.09	472.66	300.20	144.90	94.08	65.61	41.15	17.48	4.25
SD	0.00	24.84	103.56	244.45	309.43	350.02	295.92	260.80	273.49	305.25	292.70	288.09	240.85	118.83	62.87	44.95	39.56	21.13	9.04

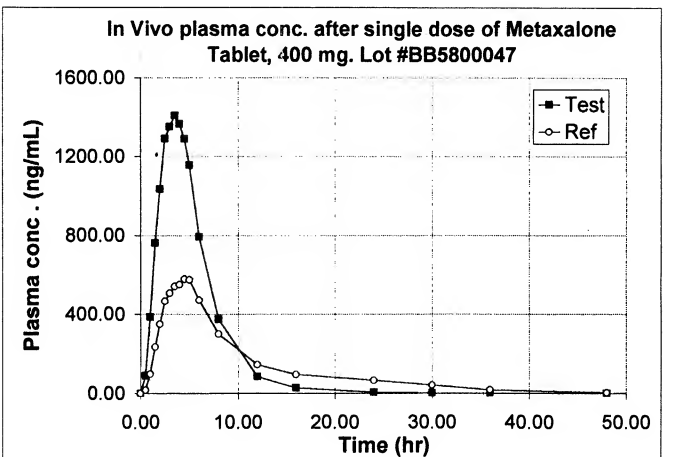


Table 4
Summary of Statistical Analysis
N=24

Log-Transformed Data

PK Variable	Least Squares Mean		Geometric Mean			Mean Square Error	Standard Error	90 % Confidence Interval (Lower Limit, Upper Limit)	P-values for ANOVA Effects		Power of ANOVA
	Test	Reference	Test	Reference	% Ratio				Product	Period	
C_{max}	7.420	6.580	1669.03	720.54	231.64	0.0758	0.0795	(202, 266)	0.0001	0.1955	0.7651
AUC_{0-t}	8.913	8.549	7428	5162	143.90	0.0513	0.0654	(129, 161)	0.0001	0.4945	0.9033
AUC_{inf}	8.925	8.604	7518	5453	137.87	0.0496	0.0643	(124, 154)	0.0001	0.5314	0.9123

Non-Transformed Data

PK Variable	Least Squares Mean				Mean Square Error	Standard Error	90 % Confidence Interval (Lower Limit, Upper Limit)	P-values for ANOVA Effects		Power of ANOVA
	Test	Reference	Difference	% Ratio				Product	Period	
C_{max}	1795.75	776.64	1019.11	231.22	160620.5255	115.6938	(206, 257)	0.0001	0.8240	0.2502
T_{max}	3.02	3.40	-0.38	88.82	0.8542	0.2668	(75.5, 102)	0.1738	0.4432	0.6820
AUC_{0-t}	8138	5672	2466.00	143.48	2614682.5587	466.7871	(129, 158)	0.0001	0.8012	0.6418
AUC_{inf}	8223	5956	2267.00	138.06	2636276.7689	468.7107	(125, 152)	0.0001	0.8248	0.6807
k_{elim}	0.3794	0.1081	0.2713	350.97	0.0147	0.0350	(296, 407)	0.0001	0.6139	0.0909
$t_{1/2}$	2.46	7.66	-5.20	32.11	8.0649	0.8198	(13.7, 50.5)	0.0001	0.2173	0.4314

Geometric means are based on least squares means of log transformed values.

ATTACHMENT 6

Solubility of Metaxalone in Deionized Water
(Results on file: NB 1202:60)

URL MUTUAL

Memorandum

From: Rakesh Grover, Ph.D.

To: Spiro Spireas, Ph.D., Vice President Research & Development

CC: Nuo Wang, Ph.D. and Diane Reed

Date: 02/22/01

Re: Metaxalone Solubility in Deionized Water

Please be advised that based on experimental work (NB1202:60), the solubility of Metaxalone in deionized water has been assessed to be approximately **0.3 mg/mL.**

Thank you.

Rakesh Grover, Ph.D.

ATTACHMENT 7

Dissolution Profiles of Metaxalone Tablets, 400 mg (Skelaxin, BB5800047 and BB5800040) in Deionized Water

Time (min)	Skelaxin	%RSD	BB5800040	%RSD	BB5800047	%RSD
0	0	0	0	0	0	0
15	6	38	2	26	4	20
30	11	12	3	23	8	17
45	21	9	6	17	10	5
60	28	8	7	16	13	5
90	39	6	8	11	18	7
120	45	5	11	11	25	21